REMARKS/ARGUMENTS

Applicants have amended claim 74 to correct dependency and have cancelled claim 91. No new matter is added by way of this amendment.

REJECTION UNDER 35 U.S.C. § 112

Claim 91 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants have cancelled this claim.

REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 71-79, 81-87, 90, 92, 96, and 98-102 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bos *et al., Proc. Am. Soc. Clin. Oncol.* Abstract #1381 (1996) ["*Bos*"] as evidenced by Herbst *et al., Expert Opin.: Biol. Ther. 1(4)*:719-731 (2001) ["*Herbst*"]. Applicants respectfully traverse this rejection.

The present invention is directed to a "second line" or "third-line" (or "fourth-line", etc.) treatment of cancer, when conventional "first-line" treatments have failed. Specifically, the present invention is directed to a method of treating cancer patients with an antibody specific and antagonistic for EGFR, wherein the patient has failed to be cured by chemotherapy or radiation.

The references relied upon by the Examiner, either separately or as a whole, fail to teach or suggest second-line treatment of the cancer patient with an anti-EGFR antibody. The art is completely silent on whether or not the patients treated therein had received previous treatments of chemotherapy or radiation, and whether the patients had failed or been resistant to these treatments.

The Examiner has ignored the standard for anticipation. Applicants need not prove that *Bos*' patients were

in fact treatment-naïve. As stated in the Office Action, the M.P.E.P. "requires the examiner to provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." (Emphasis added.) While Applicants agree that the Examiner has provided a reason why one or more patients in *Bos might* have had refractory cancer, the Examiner has not provided reasoning as to why the patients *necessarily* had refractory cancer. "Advanced cancer", as disclosed in *Bos*, is simply not synonymous with "refractory" cancer, as presently claimed.

In the Office Action dated November 2, 2007, the Examiner states that "[t]he American Cancer Society defines advanced cancer as a cancer that usually cannot be cured, and the some people develop advanced cancer after years of treatment (see copy of website page (http://www.cancer.org/docroot/CRI/content/CRI_2_4_1x_What_Is_Advanced_Cancer.asp?sitearea=)."

Applicants attach herewith a copy of the definition of "advanced cancer" from the website relied upon by the Examiner (http://www.cancer.org/docroot/CRI/content/CRI_2_4_1x_What_Is_Advanced_Cancer.asp?sitearea=). As can be seen from the attachment, "[a]dvanced cancer is cancer that has grown beyond the organ where it first started." Advanced cancer is **not** defined as cancer that has failed or been resistant to treatment with chemotherapy or radiation. Further, "advanced cancer *usually* means that the cancer can't be cured." (Emphasis added.) Advanced cancer **does not** always mean that the cancer cannot be cured with conventional treatment. In fact, "even if there is no cure, treatment can sometimes shrink the cancer, help relieve symptoms, and help you live longer. Some people can live many years with advanced cancer." Thus, advanced

cancer isn't even necessarily cancer that is resistant to treatment.

According to the American Cancer Society definition, "[f]or some people, the cancer may already be advanced when they first learn they have the disease. Other people develop advanced cancer after years of treatment." Thus, patients with advanced cancer may be patients with a late diagnosis and are treatment-naïve; *or* they may be patients with refractor cancer. *Bos* is completely silent as to which category of "advanced" the patients described therein belong.

The Office relies on *Herbst* for the proposition that one of the cancers mentioned in *Bos*, head and neck cancer, is refractory to treatment. The claims require that the tumor has failed or been resistant to chemotherapy or radiation therapy. Nowhere in *Herbst* is it taught that all head and neck cancer patients receive or are resistant to this type of therapy. In fact, according to *Herbst* at pages 719-720, "[s]tandard treatment approaches for these patients include surgery, radiation, chemoradiation, or a combination of these approaches." Thus, *Herbst* shows that one of the conventional treatments for head and neck cancer is surgery, which is not one of the treatments mentioned in the claims. Even if the head and neck patients of *Bos* did receive prior treatment, that treatment may have only been surgery, and not included chemotherapy or radiation, as presently claimed.

Thus, it does not necessarily flow that any of the patients in *Bos* had received prior, unsuccessful therapy, as required by the present claims. While it is true that some patients who have advanced cancer may also have refractory cancer, the Office has presented no evidence that all advanced cancer patients have refractory cancer.

The claims further require that the "administration is effective to inhibit growth of the refractory tumor." Nowhere

in *Bos* does it teach the tumor growth was inhibited. *Bos* reports on the results of two studies: one in which patients were given a single dose of C225 (single dose study), and one in which patients were given weekly doses (multiple dose study). In the single dose study, toxicity and pharmacokinetics were measured. In the multiple dose study, patients were given weekly doses; if patients showed no disease progression, they were given doses for up to 12 weeks.

According to *Bos*, in the single dose study "[t]wo patients with head and neck cancer had minor responses." However, *Bos* does not state what these minor responses were, and whether they related to toxicity or some other response, such as pain reduction. *Bos* does not state that tumor growth was inhibited in any patients in the single dose study.

In the multiple dose study, only five patients, out of twelve, completed the twelve-week treatment course. In other words, only five patients were without disease progression. *Bos* is silent as to whether or not these patients had stable disease before the start of the study, or whether the administration of C225 was effective to inhibit tumor growth.

Thus, not only does *Bos* fail to teach administration of EGFR antibodies to patients with *refractory* cancer, *Bos* also fails to treat inhibition of tumor growth.

Further, claims 86-87 are directed to the use of humanized antibodies. *Bos* only discusses using C225, which is a chimeric antibody, comprising a human constant region and a murine variable region. *Bos* does not teach or disclose a humanized antibody. Thus, for this additional reason, claims 86-87 are patentable over *Bos*.

Bos fails to teach inhibition of tumor growth in patients with a refractory tumor that has failed or been resistant to treatment with chemotherapy or radiation therapy. Thus, *Bos* does not anticipate the claimed invention.

Accordingly, withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 71 and 89 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Bos* as evidenced by *Herbst* in view of U.S. Patent No. 5,545,807 to Surani ["*Surani*"]. Claims 71 and 93-95 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Bos* as evidenced by *Herbst* in view of U.S. Patent No. 5,260,203 to Ladner *et al.* ["*Ladner*"]. Claims 71 and 97 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Bos* in view of Malecka-Panas *et al.*, *Hepato-Gastoenterology* 44:435-440 (1997) ["*Malecka-Panas*"] and Radinsky, *Eur J. Cancer* 31A(7/8): 1091-1095 (1995) ["*Radinsky*"]. Applicants respectfully traverse these rejections.

As outlined above, *Bos* does not teach tumor growth inhibition in patients with refractory tumors. None of the other references relied upon by the examiner cure the deficiencies of *Bos*. Even if one of ordinary skill in the art would have been motivated to try treatment of patients with refractory cancer, no reasonable expectation of success would have existed due to the complexity of treating refractory cancer.

Even if a *prima facie* case of obviousness exists, the present claims are still patentable over the prior art due to the secondary considerations of non-obviousness, including he long felt need for such a treatment and unexpected results. Applicants submit herewith the Food and Drug Administration (FDA) approved label for Erbitux® (cetuximab) ["Erbitux® label"]. Cetuximab is a chimeric antibody specific and antagonistic for EGFR. As can be seen from the enclosed label, cetuximab is approved for, *inter alia*, administration as a single agent for treatment of irinotecan- and oxaliplatin-

refractory colon cancer, and for platinum-based chemotherapy-refractory head and neck cancer. These FDA-approved methods of using cetuximab are embodiments of the present invention.

Applicants further submit herewith Venook, A., "Critical Evaluation of Current Treatments in Metastatic Colorectal Cancer", *The Oncologist 10*:250-261 (2005) ["*Venook*"]. *Venook* is a review article summarizing the state of the art regarding treatment of colon cancer published within a few years of the priority date of the captioned application.

According to *Venook* at page 250, "Fluourouracil (FU) has been the mainstay of treatment for metastatic colorectal cancer (mCRC) for many years." In fact, at page 251, *Venook* states that "[f]or more than 40 years, FU was the standard of care for patients with mCRC." Thus, patients with metastatic colorectal cancer were treated with one agent, fluourouracil, for more than four decades.

Further, "[t]he activity of FU also has been enhanced by the addition of the biochemical modulator folinic acid (leucovorin [LV]) . . . Based on better response rates, bolus FU/LV therapy became the standard of care for patients with mCRC in the U.S. and remained as such until 2000." (*Venook* 251.)

Venook then goes on to discuss the other treatments, both first-line and second-line, for mCRC which have been approved in the U.S. by the FDA in recent years. These are listed in Table 2 of *Venook*. On page 252, *Venook* discusses the newer chemotherapeutic agents irinotecan, oxaliplatin and capecitabine, which were more recently approved for mCRC treatment and which "have had a significant impact on treatment strategies for patients with mCRC."

According to Table 2, the only second-line therapy approved by the FDA around the time of the invention was irinotecan, approved in 1998. Thus, at the time of the

invention, only one option was available for patients who had failed previous treatments.

According to *Venook* at page 255, these:

> [a]dvances in chemotherapeutic agents have led to better outcomes for patients with mCRC. Chemotherapies, however, are limited by their lack of specificity and are often associated with frequent and potentially severe dose-limiting toxicities. Therefore, there is an urgent need for more effective, better-tolerated treatments that specifically target the processes pivotal to tumorigenesis and metastasis. . . The FDA recently approved two targeted agents: [including] cetuximab. . . . These two agents are already having a significant impact on mCRC treatment strategies.

Clinical trials with cetuximab in refractory colon cancer patients are discussed on pages 257 of *Venook*. According to *Venook*, the percentage of patients who responded to cetuximab therapy was 10.8% in one study. In comparison, a triple combination regimen of FU/LC plus oxaliplatin (FOLFOX), another FDA-approved second line treatment was reported to show a 9.9% (Table 1) or a 15% (p.255) response rate for refractory mCRC patients. Thus, the response rate of patients to the claimed treatment is comparable to at least one other FDA-approved treatment using three different agents. One of ordinary skill would not have expected such a high response rate in patients who had already undergone a previous unsuccessful treatment, at least based on the cited art.

Thus, as evidenced by *Venook*, one agent, FU, was the standard of care for more than 40 years for treatment of mCRC. This treatment option was supplemented with the addition of other chemotherapy agents, including irinotecan, oxaliplatin and capecitabine. Even with these supplementary treatments, there was an urgent, long-felt need for second-line therapies for treatment of refractory cancer, especially those with specificity. Cetuximab, an embodiment of the present invention, fulfills this long-felt need.

The art relied upon by the Examiner does not teach or suggest all the limitations of the present claims. Further, the art does not provide a reasonable expectation of success in arriving at the claimed invention. Even if a *prima facie* case of obviousness is established, the present invention is still patentable over the prior art, as it fulfills a long-felt need and exhibits unexpected results. Accordingly, withdrawal of this rejection is respectfully requested.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that she telephone Applicant's attorney at (908) 654-5000 in order to overcome any additional objections which she might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: November 26, 2008

Respectfully submitted,

By Andrea Jo Kamage

Andrea Jo Kamage
Registration No.: 43,703
LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP
600 South Avenue West
Westfield, New Jersey 07090
(908) 654-5000
Attorney for Applicants

919644_1.DOC

Cancer Reference Information

Detailed Guide: Advanced Cancer

What Is Advanced Cancer?

Advanced cancer is cancer that has grown beyond the organ where it first started. Often it has spread widely throughout the body (called **metastatic cancer**). Advanced cancer is not always metastatic cancer (see the section "How Is Metastatic Cancer Different from Advanced Cancer?"). But sometimes metastatic cancer is considered advanced if it is affecting a vital organ and can�t be removed.

The term advanced cancer usually means that the cancer can't be cured. But even if there is no cure, treatment can sometimes shrink the cancer, help relieve symptoms, and help you live longer. Some people can live many years with advanced cancer.

Every person�s cancer is unique. Your cancer may respond differently to treatments and grow at a different rate than the same cancer in someone else. For some people, the cancer may already be advanced when they first learn they have the disease. Other people develop advanced cancer after years of treatment. In general, advanced cancer usually occurs after you have had cancer for some time and treatment is no longer effective in stopping the growth of the cancer. But the control of symptoms often related to advanced cancer, like pain and depression, almost always continue to respond to treatment. Last Revised: 12/10/2006

The Oncologist®
Gastrointestinal Cancer

Critical Evaluation of Current Treatments in Metastatic Colorectal Cancer

ALAN VENOOK

Division of Medical Oncology, Clinical Research Office, University of California Cancer Center, San Francisco, California, USA

Key Words. Fluorouracil · Irinotecan · Oxaliplatin · Bevacizumab · Cetuximab · Vascular endothelial growth factor · VEGF

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the evolution of cancer chemotherapy for patients with colorectal cancer.
2. Discuss the current relevance of VEGF as a therapeutic target in colorectal cancer.
3. Discuss the current relevance of EGFR as a therapeutic target in colorectal cancer.

CME Access and take the CME test online and receive 1 hour of AMA PRA category 1 credit at CME.TheOncologist.com

ABSTRACT

Fluorouracil (FU) has been the mainstay of treatment for metastatic colorectal cancer (mCRC) for many years. However, in recent years, newer chemotherapeutic agents, particularly irinotecan (Campostar®; Pfizer Pharmaceuticals, New York, NY, http://www.pfizer.com) and more recently oxaliplatin (Eloxatin®; Sanofi-Aventis Inc., New York, NY, http://www.sanofi-aventis.com), have been shown to improve survival in combination with FU-based therapies. These agents were therefore incorporated into first- and second-line treatment strategies. The development of targeted agents that are tumor specific with better toxicity profiles than chemotherapeutic agents has widened the spectrum of therapies for this disease. The U.S. Food and Drug Administration (FDA) recently approved two targeted agents for treating mCRC: an antivascular endothelial growth factor monoclonal antibody (mAb), bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com), in combination with first-line 5-FU-based chemotherapy regimens and the human epidermal growth factor receptor (HER-1/EGFR)-targeted mAb cetuximab (Erbitux®; ImClone Systems, Inc., New York, NY, http://www.imclone.com) as monotherapy or in combination with irinotecan as second-line therapy in refractory cancer. These newer, more effective agents are improving clinical outcome for patients with mCRC. However, as the number of agents has increased, choosing the most effective treatment strategy has become increasingly complex. This review discusses the role of the individual agents in the treatment of mCRC and identifies the most effective regimens. *The Oncologist* 2005;10:250–261

Correspondence: Alan Venook, M.D., Division of Medical Oncology, Clinical Research Office, University of California Cancer Center, Box 1705, 1600 Divisadero, San Francisco, California 94115-1705, USA. Telephone: 415-353-9888; Fax: 415-353-9959; e-mail: venook@cc.ucsf.edu Received August 12, 2004; accepted for publication February 15, 2005.

Introduction

Colorectal cancer is the third most common cancer in the U.S., with approximately 145,000 new cases expected in 2005 [1]. Estimated 5-year survival rates range from 90% for patients with stage I disease to <10% for patients with metastatic colorectal cancer (mCRC) [1]. For many years, the standard treatment for patients with mCRC was systemic chemotherapy with fluorouracil (FU). In the past 5 years, however, therapies for mCRC have progressed dramatically and shifted from monotherapy to combination therapy and, more recently, to sequential combination therapy. Because these more efficacious treatment regimens allow patients to survive longer and receive more lines of therapy, choosing the best treatment regimen is becoming increasingly complex. This review discusses the role of various agents/regimens in the treatment of mCRC and focuses on identifying the most effective regimens based on the available data.

Chemotherapeutic Agents/Regimens for mCRC

Fluorouracil/Leucovorin

For more than 40 years, FU was the standard of care for patients with mCRC. Because FU has a schedule-dependent mode of action, various strategies have been explored to maximize its cytotoxic effects, such as changing the dose, schedule, or route of administration. A brief overview of studies follows, comparing the efficacy and toxicity profiles of different modalities.

A pooled analysis, incorporating data from six randomized trials, showed that FU administered as a continuous i.v. infusion led to a significantly higher response rate than bolus i.v. FU (Mayo Clinic protocol) (22% versus 14%, respectively; odds ratio, 0.55; $p = .0002$), although the median survival times were similar (infusional FU 12.1 months versus bolus FU 11.3 months; hazards ratio, 0.88; $p = .04$) [2]. FU administered by continuous infusion allows for the delivery of more drug than bolus FU and shifts the dose-limiting toxicity from myelosuppression to hand-foot syndrome, which results in a more favorable toxicity profile [2, 3]. The change in toxicity profile is a result of a higher concentration of FU in the bone marrow following bolus administration versus continuous infusion [4].

The activity of FU also has been enhanced by the addition of the biochemical modulator folinic acid (leucovorin [LV]). In a recent meta-analysis of 3,300 patients randomized in 19 trials, the response rate was twofold greater in patients receiving FU/LV than in those receiving FU alone (21% versus 11%, respectively; $p < .0001$) [5]. There also was a slightly, but significantly, longer survival time in those receiving FU/LV [5]. Biomodulation of FU with LV also has, however, been associated with higher incidences of grade 3 and 4 diarrhea, stomatitis, and hematologic toxicities than either bolus or infusional FU [6].

Based on better response rates, bolus FU/LV therapy became the standard of care for patients with mCRC in the U.S. and remained as such until 2000. In Europe, oncologists were, however, more likely to use a modulated infusion regimen. The most commonly used approach there is the de Gramont regimen, an every-2-weeks protocol (LVFU2) that combines bolus with infusional FU/LV. De Gramont and colleagues reported that this regimen was more effective and had a better safety profile than the LV/FU bolus regimen [7]. However, U.S. oncologists have been reluctant to

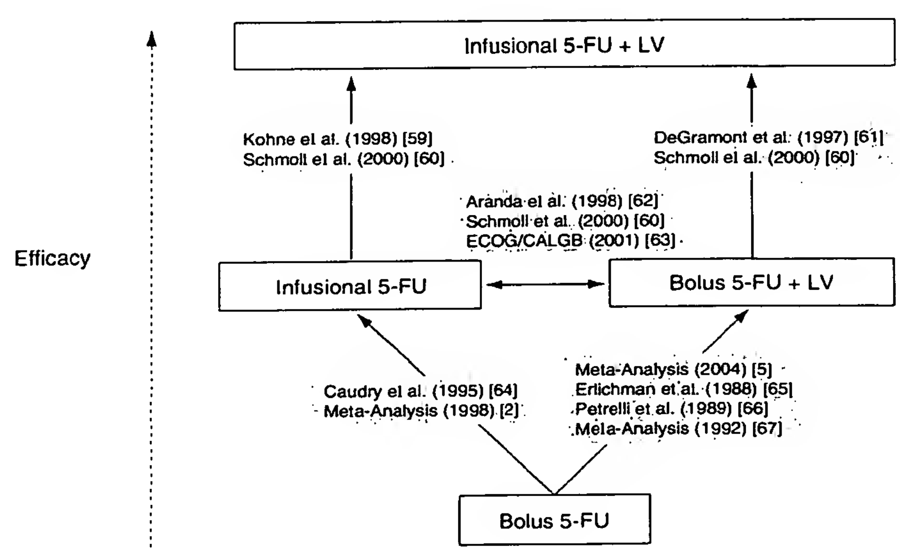


Figure 1. FU: the cornerstone of therapy for mCRC [2, 5, 59–67]. Abbreviations: CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; FU = fluorouracil; LV = leucovorin; mCRC = metastatic colorectal cancer.

use infusional FU because of the inconvenience and higher costs associated with infusion access and pumps. Figure 1 shows key publications demonstrating the efficacy of bolus versus infusional 5-FU therapy.

Irinotecan, Oxaliplatin, and Capecitabine

In the past few years, newer chemotherapeutic agents, such as irinotecan (Camptosar®; Pfizer Pharmaceuticals, New York, NY, http://www.pfizer.com), oxaliplatin (Eloxatin®; Sanofi-Aventis Inc., Paris, France, http://www.sanofi-aventis.com), and capecitabine (Xeloda®; Hoffmann-La Roche Inc., Nutley, NJ, http://www.roche.us), used as monotherapy or in combination with 5-FU-based therapy have had a significant impact on treatment strategies for patients with mCRC.

Irinotecan, a topoisomerase I inhibitor, was initially introduced as monotherapy for patients with mCRC refractory to FU [8, 9]. In two pivotal phase III trials, therapy with single-agent irinotecan resulted in a longer survival time than best supportive care or infusional FU/LV therapy in FU-refractory patients [10, 11] (Table 1). Therefore, based on these data, irinotecan was approved for patients with mCRC who had failed treatment with FU/LV (Table 2).

Table 1. The efficacy of chemotherapeutic regimens, bevacizumab in combination with IFL, and single-agent cetuximab in first- or second-line mCRC

Study	*n* of patients	Response rate (%)	Median PFS (months, unless otherwise stated)	Overall survival (months)
Irinotecan first-line treatment				
Saltz et al. 2000 [12]				
IFL	231	39[a]	7.0	14.8
Bolus FU/LV	226	21[a]	4.3	12.6
Irinotecan	226	18[a]	4.2	12.0
Douillard et al. 2000 [13]				
FOLFIRI	198	34.8[b]	6.7	17.4
FU/LV	187	21.9[b]	4.4	14.1
Koehne et al. 2003 [14]				
FOLFIRI	214	54.2	8.5	20.1
FU/LV	216	31.5	6.4	16.9
Oxaliplatin first-line treatment				
de Gramont et al. 2000 [17]				
FOLFOX	210	50.7	9.0	16.2
LVFU2	210	22.3	6.2	14.7
Goldberg et al. 2004 [19]				
FOLFOX	267	45	8.7[c]	19.5
IFL	264	31	6.9[c]	15.0
IROX	264	35	6.5[c]	17.4
Grothey et al. 2002 [20]				
FUFOX	118	48.3	7.9	20.4
Bolus FU/LV	124	22.6	5.3	16.1
Tournigand et al. 2004 [22]				
FOLFOX followed by FOLFIRI	111	FOLFOX 54% FOLFIRI 4%	10.9	20.6
FOLFIRI followed by FOLFOX	111	FOLFIRI 56% FOLFOX 15%	14.2	21.5
Capecitabine first-line treatment				
Van Cutsem et al. 2001 [26]				
Capecitabine	301	18.9	5.2	13.2
FU/LV	301	15.0	4.7	12.1
Hoff et al. 2001 [27]				
Capecitabine	302	24.8	4.3	12.5
FU/LV	303	15.5	4.7	13.3

Table 1. The efficacy of chemotherapeutic regimens, bevacizumab in combination with IFL, and single-agent cetuximab in first- or second-line mCRC (continued)

Study	*n* of patients	Response rate (%)	Median PFS (months, unless otherwise stated)	Overall survival (months)
Bevacizumab first-line treatment				
Hurwitz et al. 2004 [41]				
IFL/bevacizumab	402	44.8	10.6	20.3
IFL	411	34.8	6.2	15.6
Irinotecan second-line treatment				
Cunningham et al. 1998 [10]				
Irinotecan	189	NA	NA	9.2
BSC	90	NA	NA	6.5
Rougier et al. 1998 [11]				
Irinotecan	133	NA	4.2	10.8
FU	134	NA	2.9	8.5
Oxaliplatin second-line treatment				
Rothenberg et al. 2003 [18]				
FOLFOX	152	9.9	4.6[c]	NA
FU/LV	151	0	2.7[c]	NA
Oxaliplatin	156	1.3	1.6[c]	NA
Cetuximab second-line treatment				
Saltz et al. 2004 [57]				
Cetuximab	57	8.8	1.4	6.4

Fluorouracil is by infusion unless otherwise stated.

[a]Confirmed response rate.

[b]Intent-to-treat population.

[c]Time to disease progression

Abbreviations: BSC = best supportive care; FU = fluorouracil; FOLFIRI = fluorouracil/leucovorin plus irinotecan; FOLFOX = fluorouracil/leucovorin plus oxaliplatin; FUFOX = infusional FU/LV given weekly and every 6 weeks plus oxaliplatin; IFL = bolus fluorouracil/leucovorin plus irinotecan; IROX = irinotecan plus oxaliplatin every 3 weeks; LV = leucovorin; LVFU2 = every-2-weeks chemotherapy regimen combining bolus with infusional fluorouracil/leucovorin; mCRC = metastatic colorectal cancer; NA = not available; PFS = progression-free survival.

Table 2. FDA-approved regimens for mCRC

Regimen	U.S. approval status: First-line therapy	U.S. approval status: Second-line therapy	Year of approval
Bevacizumab plus 5-FU-based regimens (IFL, FOLFIRI, FOLFOX, and FU/LV)	√		2004
Cetuximab (monotherapy or with irinotecan)		√	2004
FOLFOX	√	√	First line, 2004; second line, 2002
FOLFIRI	√		2000
IFL	√		2000
Irinotecan		√	1998
Capecitabine monotherapy	√		2002

Abbreviations: FDA = U.S. Food and Drug Administration; FOLFIRI = fluorouracil/leucovorin plus irinotecan; FOLFOX = fluorouracil/leucovorin plus oxaliplatin; FU/LV = fluorouracil/leucovorin; IFL = bolus fluorouracil/leucovorin plus irinotecan; mCRC = metastatic colorectal cancer.

Researchers then evaluated the addition of irinotecan to FU/LV as first-line treatment for mCRC. Saltz and colleagues showed that combining irinotecan with bolus FU/LV (IFL) resulted in a higher response rate, longer progression-free survival (PFS) time, and longer overall survival time in first-line mCRC treatment compared with bolus FU/LV alone [12] (Table 1). As expected, the incidence of grade 3 diarrhea was more common with irinotecan-based therapy than with bolus FU/LV alone. Similarly, in a European trial, Douillard and colleagues also showed that adding irinotecan to weekly or every-2-weeks regimens of FU/LV by infusion (FOLFIRI) improved the response rate and increased the PFS and survival times [13] (Table 1). Based on data from these trials, the U.S. Food and Drug Administration (FDA) and European regulatory authorities approved irinotecan in combination with both bolus and infusional FU/LV as first-line therapy for mCRC, replacing FU/LV as the standard of care (Table 2). U.S. oncologists were, however, partial to the bolus regimen, and European oncologists continued to use infusional FU/LV. Interestingly, a second European trial also examined irinotecan in combination with the AIO regimen (infusional FU/LV given weekly for 6 weeks) as first-line mCRC treatment [14]. Survival times in that trial were longer than those in the Saltz et al. and Douillard et al. trials (Table 1), but this may be explained by the extensive use of second- and third-line therapies, as both oxaliplatin and irinotecan were readily available in Europe at the time.

Oxaliplatin is a cisplatin derivative with a similar mechanism of action to other platinum compounds, although its antitumor profile differs from those of cisplatin (Platinol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) and carboplatin (Paraplatin®; Bristol-Myers Squibb, http://www.bms.com) [15]. Indeed, experimental studies have shown that oxaliplatin inhibits colorectal cancer tumor cell lines that are resistant to cisplatin and carboplatin [16].

In a phase III trial, oxaliplatin was evaluated in combination with infusional FULV2 (FOLFOX regimen) as first-line therapy for patients with mCRC. The findings showed a higher response rate, longer median PFS time, and longer survival than those observed with FU/LV alone, although the survival difference was not statistically significant (Table 1) [17]. The lack of difference in survival benefit between the two groups may be explained by the small sample and crossover treatments that might have obscured any difference in survival [17]. Toxicities of oxaliplatin in combination with FU/LV2 also were mild, although dose-dependent and mostly reversible sensory neuropathy was a cumulative dose-limiting toxicity in the oxaliplatin arm. These data were submitted to the FDA in 2002, but oxaliplatin was denied approval because of the lack of a statistically significant survival benefit. A phase III trial demonstrated the efficacy of oxaliplatin-based therapy as second-line treatment for mCRC [18]. Rothenberg and colleagues showed a higher response rate and longer time to progression (TTP) with oxaliplatin plus infusional plus bolus FU than with oxaliplatin monotherapy and infusional FU/LV alone, although single-agent oxaliplatin and FU/LV had no meaningful activity (Table 1). These data led to the approval of oxaliplatin in combination with infusional FU/LV as second-line therapy following irinotecan and FU/LV for mCRC in the U.S. (Table 2).

A phase III trial recently suggested that FOLFOX first-line therapy is superior in efficacy and safety to IFL [19]. Goldberg and colleagues showed that FOLFOX produced a higher response rate (45%) and longer median survival time (19.5 months) than IFL (31% and 15 months, respectively) and than irinotecan and oxaliplatin given every 3 weeks (IROX; 35% and 17.4% months, respectively) (Table 1). With the exception of peripheral neuropathy, the toxicity profile for FOLFOX also was more favorable than that of either IFL or IROX.

The conclusion that the FOLFOX regimen is more effective than IFL or IROX for first-line mCRC therapy must be tempered by several nuances in the trial design. Notably, that an infusional FU-based combination regimen was compared with a bolus FU-based combination regimen, and therefore the individual contributions of irinotecan and oxaliplatin to an FU-based regimen cannot be determined. Also, crossover to second-line therapy was imbalanced because oxaliplatin was not readily available in the U.S. at the time of the trial, and therefore, most patients who received FOLFOX initially, as first-line therapy, received irinotecan at progression, whereas only a few patients who received first-line IFL received oxaliplatin at progression. The FDA, however, recently approved oxaliplatin as first-line therapy for mCRC (Table 2). In Europe, a second trial examined the AIO regimen plus oxaliplatin (FUFOX) versus bolus FU/LV in patients with advanced CRC [20]. It was shown that the oxaliplatin-based regimen significantly improved response rate, but not overall survival, although survival was longer (20.4 months versus 16.1 months) with the FUFOX regimen (Table 1). As with other European trials during that period, the long overall survival time may be attributed to the 75% of patients who received oxaliplatin- and/or irinotecan-based salvage therapies [20].

FOLFOX and FOLFIRI appear to be the most effective in terms of efficacy and tolerability. In a recent randomized trial, Colucci and colleagues showed that the two regimens were comparable [21]. Larger randomized studies comparing FOLFOX with FOLFIRI are ongoing and will help us to evaluate which is the more effective regimen.

Tournigand and colleagues also evaluated the FOLFOX and FOLFIRI regimens to find the best sequence for treating patients with mCRC [22]. Those authors showed that a sequence of first-line FOLFOX followed by second-line

FOLFIRI resulted in a similar survival time to that produced by the reverse sequence (Table 1). However, as at least 30% of patients did not receive second-line therapy, the authors highlighted the importance of choosing the most appropriate first-line therapy. Although both first-line therapies achieved similar response rates (FOLFIRI 56% versus FOLFOX 54%), second-line FOLFIRI achieved a significantly lower response rate than did FOLFOX (4% versus 15%). The toxicity profiles for the two regimens were also different. As expected from previous studies, grade 3/4 mucositis, nausea/vomiting, and grade 2 alopecia were more common with FOLFIRI, whereas grade 3/4 neutropenia and neurosensory toxicity were more common with FOLFOX. The authors noted that future studies should focus on the limitations of the trial, notably that neurotoxicity forces many patients to stop oxaliplatin before tumor resistance develops and that FOLFIRI has a relatively poor efficacy as a second-line therapy.

Importantly, it should be noted that phase III trials evaluating combination therapy have reported median overall survival times in the range of 14.8–21.5 months. As these were large, randomized trials conducted over a relatively short period, it is unlikely that patient selection or other factors outside the treatment strategy were responsible for these differences. It is most likely that second- or third-line therapies had an impact on overall survival. A recent meta-analysis analyzed results from seven phase III trials in mCRC to correlate the percentage of patients receiving: A) second-line therapy, and B) all three agents with the reported median overall survival [23]. The median overall survival was significantly correlated with the percentage of patients receiving all three agents over the disease course, but not with the proportion of patients receiving second-line therapy. To optimize clinical outcome, the authors suggested that it is important to make FU/LV, irinotecan, and oxaliplatin available to all patients with mCRC who are candidates for this type of therapy. However, possible study bias was noted, that is, patients who lived longer had a better chance of receiving all therapies, while patients with poorer performance statuses and shorter life expectancies were probably excluded from second-line therapy. Also, this analysis could not evaluate the best sequence of treatment, although ongoing and future randomized trials comparing different sequences should address these questions. Finally, as sequential therapies cannot be predefined in treatment protocols, overall survival may no longer be regarded as the most sensitive end point for assessing the efficacy of first-line therapy; other factors, such as PFS and TTP, should be considered.

Researchers are investigating alternative approaches to optimizing FU therapy. Capecitabine is an oral fluoropyrimidine carbamate, initially designed to deliver FU predominantly to tumor cells [24, 25]. In two randomized trials, the efficacy and toxicity of capecitabine as first-line treatment in patients with mCRC were evaluated [26, 27] (Table 1). Those trials showed that capecitabine had an efficacy that was at least equivalent to that of i.v. FU/LV. Grade 3 hand-foot syndrome was reported more frequently with capecitabine, although the condition was tolerated with a reduced dose. A higher incidence of grade 3/4 hyperbilirubinemia also was reported, but all cases were reversible. Against this background, capecitabine appears to offer equivalent efficacy and a better toxicity profile than the Mayo regimen, with the added convenience of an oral agent. Based on these data, capecitabine was approved in the U.S. as first-line therapy for patients with mCRC for whom combination therapy is not warranted (Table 2). Other phase II studies have examined the addition of oxaliplatin or irinotecan to capecitabine [28, 29]. So far, data have been encouraging, with toxicity profiles similar to that of infusional FU, and it appears that oxaliplatin/capecitabine is equivalent to irinotecan/ capecitabine therapy. Based on these data, randomized, phase III trials are planned to evaluate oxaliplatin or irinotecan in combination with capecitabine in patients with mCRC.

Targeted Agents in Combination with Chemotherapy—Moving Forward

Advances in chemotherapeutic agents have led to better outcomes for patients with mCRC. Chemotherapies, however, are limited by their lack of specificity and are often associated with frequent and potentially severe dose-limiting toxicities. Therefore, there is an urgent need for more effective, better-tolerated treatments that specifically target the processes pivotal to tumorigenesis and metastasis. Further advances in the understanding of molecular biology have led to the development of target-specific agents. The FDA recently approved two targeted agents: an antivascular endothelial growth factor (anti-VEGF) monoclonal antibody (mAb), bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com), and a human epidermal growth factor receptor (HER-1/EGFR)-targeted mAb, cetuximab (Erbitux®; Imclone Systems, Inc., New York, NY, http://www.imclone.com), as first- and second-line mCRC therapy, respectively. These two agents are already having a significant impact on mCRC treatment strategies.

Bevacizumab

Rationale for Targeting VEGF

Over 20 years ago, researchers showed that tumors cannot grow beyond 1–2 mm without the establishment of a blood supply [30]. The formation of tumor blood vessels, or angiogenesis, not only allows tumors to absorb nutrients

and oxygen for their further growth and development but also allows a pathway for migrating tumor cells to access the systemic circulation and establish metastases. The transition, or switch, of a tumor to an angiogenic phenotype is caused by an increase in proangiogenic factors, including VEGF, basic fibroblast growth factor (bFGF), and transforming growth factor beta (TGF-β), and a decrease in antiangiogenic factors, such as interferon-α [31].

VEGF is a specific mitogen for the endothelial cell and one of the most potent proangiogenic factors. VEGF acts as a survival factor for endothelial cells through the inhibition of apoptosis and plays an important role in mobilizing endothelial cell precursors to sites of angiogenesis [32, 33]. VEGF is upregulated in most human tumors, including colorectal cancer [33]. This has been correlated with increased tumor invasion, microvessel density, disease recurrence, and a poor prognosis [34, 35]. Based on these observations, and its low levels in healthy tissue, VEGF appears to be a particularly attractive target for anticancer therapy.

There are a variety of strategies that target VEGF, although VEGF blockade with mAbs is the most studied approach. Bevacizumab is an anti-VEGF, humanized mAb that is the most advanced agent of its class in clinical development. Preclinical data show that this agent is active in colorectal cancer and other types of solid tumors and is better tolerated than conventional chemotherapeutic agents [36, 37]. Preclinical studies have also shown that combining anti-VEGF therapy with chemotherapeutic agents results in augmented antitumor activity [38, 39]. The mechanism by which bevacizumab enhances the efficacy of chemotherapy is not well understood, although it has been proposed that, as tumor blood vessels are chaotic, irregular, and leaky, relatively low doses of anti-VEGF therapy "normalize" tumor vasculature, reducing intratumoral pressure and allowing better delivery of therapeutic agents to the tumor, thereby maximizing antitumor activity [40]. Against this background, it was suggested that the most effective use of bevacizumab is in combination with chemotherapy.

Clinical Studies

Several studies have examined bevacizumab in combination with chemotherapy in the first- and second-line settings in patients with mCRC. Phase II and III trials of bevacizumab in combination with FU/LV and IFL are completed or ongoing (Table 1 and Table 3). Studies of bevacizumab in combination with oxaliplatin-based therapies are ongoing.

The phase III trial was the first phase III evaluation of the efficacy and safety of first-line bevacizumab and led to the recent approval of this agent in combination with i.v. FU-based therapy as first-line therapy for patients with mCRC (Table 2) [41]. In this trial, Hurwitz and colleagues examined bevacizumab in combination with IFL as first-line therapy for patients with mCRC. Over 900 patients were randomized to one of three treatments: IFL/placebo, IFL/bevacizumab, or FU/LV/bevacizumab. The FU/LV/bevacizumab arm was included because no previous study had examined IFL in combination with bevacizumab, but this arm was stopped when the safety of bevacizumab plus IFL was demonstrated in an interim analysis. Treatment could continue until disease progression, unacceptable toxicity, or 96 weeks. At progression, patients could receive second-line therapy. Oncologists treating patients in a bevacizumab-containing arm could choose to continue with bevacizumab during second-line therapy.

The addition of bevacizumab to IFL resulted in a significantly longer survival time, by almost 5 months (30% increase in survival) (20.3 months versus 15.6 months; $p < .001$) (Table 1 and Table 3). The addition of bevacizumab

Table 3. Completed or ongoing trials evaluating bevacizumab in combination with bolus FU/LV therapy in mCRC

Study	*n* of patients	Response rate (%)	Median PFS (months)	Overall survival (months)
Kabbinavar et al. 2003 [43]				
FU/LV/bevacizumab (high-dose)	33	24	7.2	16.1
FU/LV/bevacizumab (low-dose)	35	40	9.0	21.5
FU/LV	36	17	5.2	13.8
Kabbinavar et al. 2004 [44]				
FU/LV/bevacizumab	105	26	9.2	16.6
FU/LV	104	15	5.5	12.9
Hurwitz et al. 2004 [45]				
FU/LV/bevacizumab	110	40	8.8	18.3
IFL	100	37	6.8	15.1

Abbreviations: FU/LV = fluorouracil/leucovorin; IFL = bolus fluorouracil/leucovorin plus irinotecan; mCRC = metastatic colorectal cancer; PFS = progression-free survival

to IFL also resulted in a significantly greater overall response rate, duration of response, and PFS time. Survival benefit was observed for all patient subgroups and was independent of second-line therapy. For the subgroup of patients who received second-line therapy with oxaliplatin-containing regimens, overall survival times were 25.1 months and 22.2 months for the IFL/bevacizumab and IFL/placebo arms, respectively [42].

Overall, IFL with bevacizumab was generally well tolerated, with no overlapping toxicities. Although a number of adverse events, including bleeding, thrombosis, proteinuria, and hypertension, were observed in phase I/II trials, only hypertension (easily managed with standard blood pressure medications) had a higher incidence in the IFL/bevacizumab arm. However, six patients (1.5%) receiving IFL/bevacizumab had gastrointestinal events, including bowel perforation. Although this event was uncommon given the size of the trial, the risk of such events may be increased with bevacizumab. Studies are ongoing to understand further bevacizumab-related gastrointestinal perforation.

Phase II and III studies have evaluated the addition of bevacizumab to FU/LV as another standard option for the first-line treatment of mCRC [43–45] (Table 3). Indeed, these studies showed that FU/LV/bevacizumab compares favorably with FU/LV. Therefore, bevacizumab should be considered for the subgroup of patients for whom irinotecan- or oxaliplatin-based therapy is not recommended, as this subgroup of patients has few treatment options available.

Clinical trials are in progress or planned to evaluate the addition of bevacizumab to FOLFOX or FOLFIRI. For example, a recently completed phase III trial evaluated the addition of bevacizumab to FOLFOX in the second-line treatment of patients who have failed previous irinotecan plus FU therapy. Analyses of the findings are ongoing, but these data demonstrated that patients receiving bevacizumab plus FOLFOX had a 17% longer survival time than those receiving FOLFOX alone (12.5 months versus 10.7 months) and this regimen also had an acceptable toxicity profile [46]. Therefore, adding bevacizumab to chemotherapy results in a significant survival benefit for patients with untreated or relapsed mCRC. Figure 2 shows the survival benefit of bevacizumab plus chemotherapy relative to other regimens and best supportive care.

Other ongoing trials will provide further information on the efficacy and safety of bevacizumab in different settings. These studies will help us to define the extent to which bevacizumab can be used to treat mCRC. Finally, studies are examining bevacizumab plus FOLFOX in the adjuvant setting. This is a particularly important setting for antiangiogenic therapy, as targeting tumor neovasculature during early disease may contribute to curative treatment.

Cetuximab

Rationale for Targeting HER-1/EGFR

The HER-1/EGFR signaling pathway is thought to play a pivotal role in tumor growth and progression of various cancers, including colorectal cancer [47]. HER-1/EGFR belongs to the HER family of receptors. These receptors are transmembrane glycoproteins, comprising an extracellular ligand-binding domain, an intracellular tyrosine-kinase (TK) domain, and a transmembrane segment [47]. Various ligands can bind to the HER-1/EGFR extracellular domain inducing receptor homo- or heterodimerization with another HER-1/ EGFR receptor or other HER family members. This results in activation of the receptor's TK activity, initiating a downstream signaling cascade that ultimately leads to tumor cell proliferation, migration, adhesion and angiogenesis, and inhibition of apoptosis [48].

Various reports have shown that HER-1/EGFR signaling is dysregulated in colorectal cancer and other tumor types [49]. HER-1/EGFR overexpression has also been correlated with disease progression, poor prognosis, and reduced sensitivity to chemotherapy [50]. Therefore, several strategies have been developed to target HER-1/EGFR, including small-molecule TK inhibitors and mAbs. Cetuximab is the most advanced mAb targeting HER-1/EGFR in clinical development.

Cetuximab exerts its antitumor effects through ligand-independent processes, stimulating receptor internalization [51]. Preclinical and early clinical studies have shown that single-agent cetuximab primarily leads to cytostatic activity, whereas combining cetuximab with chemotherapeutic agents, such as cisplatin, topotecan (Hycamtin®; GlaxoSmithKline, Philadelphia, PA, http://www.gsk.com), and irinotecan leads to synergistic antitumor activity [51–54]. One hypothesis for this synergy is that, for the majority of cell lines, blocking HER-1/ EGFR signaling is insufficient for cytotoxicity, but HER-1/ EGFR inhibition may leave the cells more vulnerable to chemotherapy. Importantly, these studies consistently suggested that, at least in these models, HER-1/EGFR expression is required for cetuximab activity.

Clinical Data

A phase II study evaluated the activity and safety of cetuximab plus irinotecan in patients with irinotecan-refractory CRC. The response rate was 22.5% in 120 patients who had progressive disease on irinotecan [55]. Cunningham and colleagues also evaluated cetuximab alone and cetuximab plus irinotecan in patients with irinotecan-refractory CRC [56]. The response rates were 10.8% for cetuximab alone and 22.9% for cetuximab plus irinotecan. Finally, a more recent phase II trial also assessed the safety and efficacy of single-agent cetuximab in patients with chemotherapy-refractory mCRC who express HER-1/EGFR [57]. The findings were

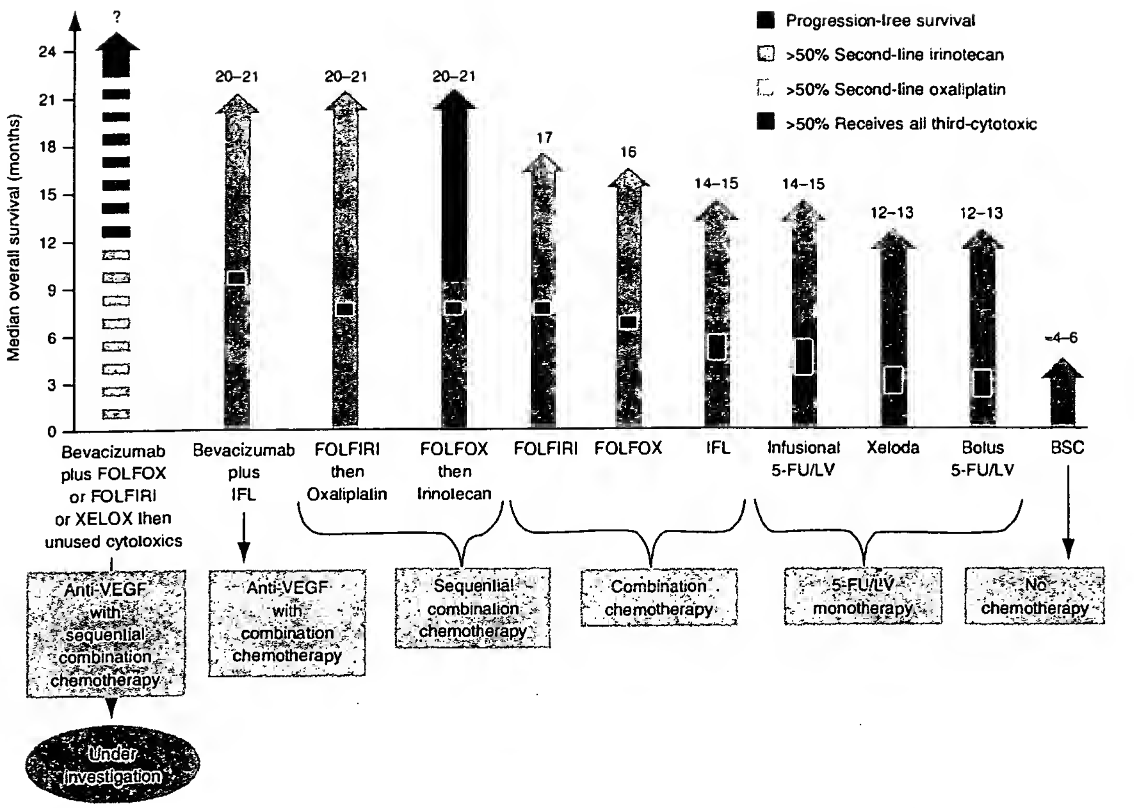


Figure 2. Survival benefit of bevacizumab plus first-line chemotherapy relative to other treatment strategies in patients with mCRC. Abbreviations: BSC = best supportive care; FOLFIRI = fluorouracil/leucovorin plus irinotecan; FOLFOX = every-2-weeks chemotherapy regimen combining bolus with infusional fluorouracil/leucovorin plus oxaliplatin; FU/LV = fluorouracil/leucovorin; IFL = bolus fluorouracil/leucovorin plus irinotecan; mCRC = metastatic colorectal cancer; VEGF = vascular endothelial growth factor; XELOX = capecitabine plus oxaliplatin.

similar to those of previous trials (Table 1). Unfortunately, response did not correlate with the degree of HER-1/EGFR expression as predicted by preclinical studies. This may be a result of the imprecision of quantifying HER-1/EGFR expression or possibly because HER-1/EGFR may not be the most appropriate marker for predicting response to therapy. Techniques such as gene expression profiling may help us to identify predictive markers of response, allowing the selection of patients most likely to respond to therapy.

Although different trials, particularly those with different regimens, should be compared with caution, the response rate from this trial was equivalent to the level of activity observed with second-line FOLFOX (9.9%) [18]. Based on these data, cetuximab was recently approved as second-line therapy for patients with mCRC in the U.S. and Europe (Table 2).

The side effects observed in this trial were manageable and similar to those previously reported. The most commonly reported grade 3/4 adverse events were severe hypersensitivity (managed with standard medications) and asthenia, fatigue, malaise, or lethargy. An acne-like rash typically associated with HER-1/EGFR inhibition was also observed in almost every patient, but none of the patients discontinued treatment because of the rash.

Finally, pilot trials have evaluated cetuximab in combination with IFL as first-line therapy for mCRC [58], and randomized phase III trials are examining cetuximab in combination with chemotherapy as first-line and adjuvant therapy. These studies will provide further information on the role of cetuximab in the treatment of CRC.

Conclusions

We have discussed some of the results from recently completed trials examining various chemotherapeutic regimens and/or targeted agents as first- and second-line mCRC therapy. We can conclude that the development of newer agents and the shift in treatment from monotherapy to sequential combination chemotherapy has improved clinical outcome for patients with mCRC, but the most appropriate setting for each of these agents/regimens still needs to be determined.

In terms of efficacy and tolerability, FOLFOX, FOLFIRI, and IFL plus bevacizumab are the most effective first-line regimens. However, we still cannot confirm which of these

regimens is the most effective for individual patients, although bevacizumab plus FOLFOX or FOLFIRI is likely to have the most clinical benefit (Fig. 2). In addition, important issues regarding the most effective sequence for these agents/regimens in the second- and third-line settings have yet to be clarified. For example, if patients progress after IFL, their options for second-line treatment include bevacizumab plus FOLFOX, cetuximab plus irinotecan, and capecitabine plus oxaliplatin. Recently, Grothey and colleagues [20] suggested that sequence is less important if all treatments are made available to all patients with mCRC. Ongoing, well-designed, comparative trials will hopefully provide a better understanding of how each regimen should be used to achieve maximum clinical benefit.

In addition, the optimal chemotherapy combinations, doses, and sequences of administration have yet to be defined. The addition of targeted agents has only added to the complexity. Indeed, it is likely that the optimal dose may vary with tumor location, growth rate, and previous therapy. Therefore, further studies are required to define the optimal dose and regimens for these agents in mCRC.

FU has been the cornerstone of treatment for mCRC for over 40 years. In the past few years, the introduction of more effective chemotherapeutic agents and targeted agents with their promising activities and mild toxicity profiles has pushed the overall median survival time from 12 months to 2 years. However, as discussed, there are still many challenges facing oncologists. Research is ongoing to understand these issues, and significant advances are expected through the implementation of well-designed clinical trials and continued preclinical investigation.

Disclosure of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

References

1 American Cancer Society. Cancer facts and figures. Atlanta, GA: American Cancer Society, 2005. http://www.cancer.org/downloads/STT/CAFF2005f4PWSecured.pdf. Accessed March 8, 2005.

2 Meta-analysis Group In Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 1998;16:301–308.

3 Perry M. The Chemotherapy Source Book. Philadelphia: Lippincott Williams & Wilkins, 1999:1–534.

4 Fraile RJ, Baker LH, Buroker TR et al. Pharmacokinetics of 5-fluorouracil administered orally, by rapid intravenous and by slow infusion. Cancer Res 1980;40:2223–2228.

5 Thirion P, Michiels S, Pignon JP et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. The Meta-Analysis Group in Cancer. J Clin Oncol 2004;22:3766–3775.

6 Kohne CH, Wils J, Lorenz M et al. Randomized phase III study of high-dose fluorouracil given as a weekly 24-hour infusion with or without leucovorin versus bolus fluorouracil plus leucovorin in advanced colorectal cancer: European Organization of Research and Treatment of Cancer Gastrointestinal Group Study 40952. J Clin Oncol 2003;21:3721–3728.

7 de Gramont A, Bosset JF, Milan C et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol 1997;15:808–815.

8 Hsiang YH, Hertzberg R, Hecht S et al. Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. J Biol Chem 1985;260:14873–14878.

9 Van Cutsem E, Rougier P, Droz J et al. Clinical benefit of irinotecan (CPT-11) in metastatic colorectal cancer (CRC) resistant to 5-FU. Proc Am Soc Clin Oncol 1997;8:268a.

10 Cunningham D, Pyrhonen S, James RD et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 1998;352:1413–1418.

11 Rougier P, Van Cutsem E, Bajetta E et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998;352:1407–1412.

12 Saltz LB, Cox JV, Blanke C et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 2000;343:905–914.

13 Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000;355:1041–1047.

14 Koehne C, Van Cutsem E, Wils J et al. Irinotecan improves the activity of the AIO regimen in metastatic colorectal cancer: results of EORTC GI Group Study 40986. Proc Am Soc Clin Oncol 2003;22:254a.

15 Woynarowski JM, Chapman WG, Napier C et al. Sequence- and region-specificity of oxaliplatin adducts in naked and cellular DNA. Mol Pharmacol 1998;54:770–777.

16 Rixe O, Ortuzar W, Alvarez M et al. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. Biochem Pharmacol 1996;52:1855–1865.

17 de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938–2947.

18 Rothenberg ML, Oza AM, Bigelow RH et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol 2003;21:2059–2069.

19 Goldberg RM, Sargent DJ, Morton RF et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23–30.

20 Grothey A, Deschler B, Kroening H et al. Phase III study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo) vs weekly high-dose 24h 5-FU infusion/FA + oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). Proc Am Soc Clin Oncol 2002;21:129a.

21 Colucci G, Maiello E, Gebbia V et al. Preliminary results of a randomized multicenter trial of the Gruppo Oncologico Italia Meridionale (GOIM) comparing FOLFIRI vs FOLFOX in advanced colorectal (ACC) patients. Proc Am Soc Clin Oncol 2003;22:255a.

22 Tournigand C, Andre T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229–237.

23 Grothey A, Sargent D, Goldberg RM et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 2004;22:1209–1214.

24 Ishikawa T, Utoh M, Sawada N et al. Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts. Biochem Pharmacol 1998;55:1091–1097.

25 Miwa M, Ura M, Nishida M et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 1998;34:1274–1281.

26 Van Cutsem E, Twelves C, Cassidy J et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19:4097–4106.

27 Hoff PM, Ansari R, Batist G et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 2001;19:2282–2292.

28 Van Cutsem E, Twelves C, Tabernero JM et al. XELOX: mature results of a multinational, phase II trial of capecitabine plus oxaliplatin, an effective 1st line option for patients (pts) with metastatic colorectal cancer. Proc Am Soc Clin Oncol 2003;22:255a.

29 Patt Y, Lin E, Leibmann J et al. Capecitabine plus irinotecan for chemotherapy-naive patients with metastatic colorectal cancer (MCRC): US multicenter phase II trial. Proc Am Soc Clin Oncol 2003;22:281a.

30 Folkman J. Tumor angiogenesis. Adv Cancer Res 1974;19:331–358.

31 Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996;86:353–364.

32 Ferrara N. Role of vascular endothelial growth factor in regulation of physiological angiogenesis. Am J Physiol Cell Physiol 2001;280:C1358–C1366.

33 Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. Endocr Rev 1997;18:4–25.

34 Frank RE, Saclarides TJ, Leurgans S et al. Tumor angiogenesis as a predictor of recurrence and survival in patients with node-negative colon cancer. Ann Surg 1995;222:695–699.

35 Choi HJ, Hyun MS, Jung GJ et al. Tumor angiogenesis as a prognostic predictor in colorectal carcinoma with special reference to mode of metastasis and recurrence. Oncology 1998;55:575–581.

36 Warren RS, Yuan H, Matli MR et al. Regulation by vascular endothelial growth factor of human colon cancer tumorigenesis in a mouse model of experimental liver metastasis. J Clin Invest 1995;95:1789–1797.

37 Gerber HP, Hillan KJ, Ryan AM et al. VEGF is required for growth and survival in neonatal mice. Development 1999;126:1149–1159.

38 Hu L, Hofmann J, Zaloudek C et al. Vascular endothelial growth factor immunoneutralization plus paclitaxel markedly reduces tumor burden and ascites in athymic mouse model of ovarian cancer. Am J Pathol 2002;161:1917–1924.

39 Sweeney CJ, Miller KD, Sissons SE et al. The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. Cancer Res 2001;61:3369–3372.

40 Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005;307:58-62.

41 Hurwitz HI, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–2342.

42 Hedrick E, Hurwitz HI, Sarkar S et al. Post-progression therapy (PPT) effect on survival in AVF2107, a phase III trial of bevacizumab in first-line treatment of metastatic colorectal cancer (mCRC). Proc Am Soc Clin Oncol 2004;23:249a.

43 Kabbinavar F, Hurwitz HI, Fehrenbacher L et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003;21:60–65.

44 Kabbinavar F, Schulz J, McCleod M et al. Bevacizumab (Avastin), a monoclonal antibody to vascular endothelial growth factor, prolongs progression free survival in first-line colorectal cancer (CRC) in subjects who are not suitable candidates for first-line CPT-11. Proc Am Soc Clin Oncol 2004;23:249a.

45 Hurwitz HI, Fehrenbacher L, Hainsworth J et al. Bevacizumab in combination with 5-fluorouracil and leucovorin: a promising regimen for first-line metastatic colorectal cancer. Proc Gastrointest Cancer Symp 2004:182a.

46 Mitchell EP, Alberts SR, Schwartz MA et al. High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: results from the Eastern Cooperative Oncology Group (ECOG) study E3200. Proc Gastrointest Cancer Symp 2005.

47 Wells A. EGF receptor. Int J Biochem Cell Biol 1999;31:637–643.

48 Arteaga CL. The epidermal growth factor receptor: from mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia. J Clin Oncol 2001;19(suppl 18):32S–40S.

49 Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. Eur J Cancer 2001;37(suppl 4):S9–S15.

50 Mendelsohn J, Baselga J. The EGF receptor family as targets for cancer therapy. Oncogene 2000;19:6550–6565.

51 Fan Z, Baselga J, Masui H et al. Antitumor effect of anti-epidermal growth factor receptor monoclonal antibodies plus cis-diamminedichloroplatinum on well established A431 cell xenografts. Cancer Res 1993;53:4637–4642.

52 Baselga J, Pfister D, Cooper MR et al. Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. J Clin Oncol 2000;18:904–914.

53 Ciardiello F, Bianco R, Damiano V et al. Antitumor activity of sequential treatment with topotecan and anti-epidermal growth factor receptor monoclonal antibody C225. Clin Cancer Res 1999;5:909–916.

54 Prewett MC, Hooper AT, Bassi R et al. Enhanced antitumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in combination with irinotecan (CPT-11) against human colorectal tumor xenografts. Clin Cancer Res 2002:8:994–1003.

55 Saltz B, Rubin M, Hochster H et al. Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR). Proc Am Soc Clin Oncol 2001;20:2a.

56 Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337–345.

57 Saltz LB, Meropol NJ, Loehrer PJ Sr. et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004;22:1201–1208.

58 Folprecht G, Lutz M, Schoeffski P et al. Cetuximab/irinotecan/high-dose-5-fluorouracil/leucovorin (HD-5-FU/LV) in the first-line therapy of metastatic colorectal cancer (CRC). Proc Gastrointest Cancer Symp 2004:142.

59 Kohne CH, Schoffski P, Wilke H et al. Effective biomodulation by leucovorin of high-dose infusion fluorouracil given as a weekly 24-hour infusion: results of a randomized trial in patients with advanced colorectal cancer. J Clin Oncol 1998;16:418–426.

60 Schmoll HJ, Kohne C, Lorenz M et al. Weekly 24h infusion of high-dose (HD) 5-fluorouracil (5-FU24h) with or without folinic acid (FA) vs bolus 5-FU/FA (NCCTG/Mayo) in advanced colorectal cancer (CRC): a randomized phase III study of the EORTC Gastrointestinal Tract Cancer Cooperative Group and the AIO. J Clin Oncol 2000;19:241a.

61 de Gramont A, Louvet C, Andre T. A simplified bimonthly regimen with leucovorin and 5-fluorouracil for metastatic colorectal cancer. Proc Am Soc Clin Oncol 1997;16:287a.

62 Aranda E, Diaz-Rubio E, Cervantes A et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with weekly high-dose 48-hour continuous-infusion fluorouracil for advanced colorectal cancer: a Spanish Cooperative Group for Gastrointestinal Tumor Therapy (TTD) study. Ann Oncol 1998;9:727–731.

63 O'Dwyer PJ, Manola J, Valone FH et al. Fluorouracil modulation in colorectal cancer: lack of improvement with N-phosphonoacetyl-l-aspartic acid or oral leucovorin or interferon, but enhanced therapeutic index with weekly 24-hour infusion schedule—an Eastern Cooperative Oncology Group/Cancer and Leukemia Group B Study. J Clin Oncol 2001;19:2413–2421.

64 Caudry M, Bonnel C, Floquet A et al. A randomized study of bolus fluorouracil plus folinic acid versus 21-day fluorouracil infusion alone or in association with cyclophosphamide and mitomycin C in advanced colorectal carcinoma. Am J Clin Oncol 1995;18:118–125.

65 Erlichman C, Fine S, Wong A et al. A randomized trial of fluorouracil and folinic acid in patients with metastatic colorectal carcinoma. J Clin Oncol 1988;6:469–475.

66 Petrelli N, Douglass HO Jr, Herrera L et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. Gastrointestinal Tumor Study Group. J Clin Oncol 1989;7:1419–1426.

67 Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 1992;10:896–903.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Erbitux safely and effectively. See full prescribing information for Erbitux.

Erbitux® (cetuximab)
Solution for intravenous use
Initial U.S. Approval: 2004

> **WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST**
>
> ***See full prescribing information for complete boxed warning.***
>
> - **Serious infusion reactions, some fatal, occurred in approximately 3% of patients. (5.1)**
> - **Cardiopulmonary arrest and/or sudden death occurred in 2% of patients receiving Erbitux in combination with radiation therapy. (5.2, 5.6)**

---------------RECENT MAJOR CHANGES---------------

Warnings and Precautions

Infusion Reactions (5.1)	09/2008
Dermatologic Toxicity (5.4)	09/2008

---------------INDICATIONS AND USAGE---------------

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy. (1.1, 14.1)
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. (1.1, 14.1)

Colorectal Cancer

- As a single agent, EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan-based regimens. (1.2, 14.2)
- In combination with irinotecan, EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Approval is based on objective response rate; no data are available demonstrating an improvement in increased survival. (1.2, 14.2)

--------------DOSAGE AND ADMINISTRATION--------------

- Premedicate with an H_1 antagonist. (2.3)
- Administer 400 mg/m² initial dose as a 120-minute intravenous infusion followed by 250 mg/m² weekly infused over 60 minutes. (2.1, 2.2)
- Initiate Erbitux (cetuximab) one week prior to initiation of radiation therapy. (2.1)
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grades 3–4 infusion reactions. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneform rash. Reduce dose for recurrent, severe rash. (2.4)

-------------DOSAGE FORMS AND STRENGTHS-------------

- 100 mg/50 mL, single-use vial (3)
- 200 mg/100 mL, single-use vial (3)

----------------CONTRAINDICATIONS----------------

None (4)

--------------WARNINGS AND PRECAUTIONS--------------

- **Infusion Reactions:** Immediately stop and permanently discontinue Erbitux for serious infusion reactions. Monitor patients following infusion. (5.1)
- **Cardiopulmonary Arrest:** Closely monitor serum electrolytes during and after Erbitux. (5.2, 5.6)
- **Pulmonary Toxicity:** Interrupt therapy for acute onset or worsening of pulmonary symptoms. (5.3)
- **Dermatologic Toxicity:** Limit sun exposure. Monitor for inflammatory or infectious sequelae. (2.4, 5.4)

----------------ADVERSE REACTIONS----------------

The most common adverse reactions (incidence ≥25%) are: cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-------------USE IN SPECIFIC POPULATIONS-------------

- **Pregnancy:** Administer Erbitux to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. (8.1)
- **Nursing Mothers:** Discontinue nursing during and for 60 days following treatment with Erbitux. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

Infusion Reactions: Serious infusion reactions occurred with the administration of Erbitux in approximately 3% of patients in clinical trials, with fatal outcome reported in less than 1 in 1000. [See *Warnings and Precautions (5.1)* and *Adverse Reactions (6)*.] Immediately interrupt and permanently discontinue Erbitux infusion for serious infusion reactions. [See *Warnings and Precautions (5.1)* and *Dosage and Administration (2.4)*.]

Cardiopulmonary Arrest: Cardiopulmonary arrest and/or sudden death occurred in 2% of 208 patients with squamous cell carcinoma of the head and neck treated with radiation therapy and Erbitux. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux. [See *Warnings and Precautions (5.2, 5.6)*.]

1 INDICATIONS AND USAGE

1.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Erbitux® (cetuximab) is indicated in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck. [See *Clinical Studies (14.1)*.]

Erbitux, as a single agent, is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed. [See *Clinical Studies (14.1)*.]

1.2 Colorectal Cancer

Erbitux, as a single agent, is indicated for the treatment of EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens. Erbitux, as a single agent, is also indicated for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan-based regimens. [See *Clinical Studies (14.2)* and *Warnings and Precautions (5.7)*.]

Erbitux, in combination with irinotecan, is indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. The effectiveness of Erbitux in combination with irinotecan is based on objective response rates. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Erbitux in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal carcinoma. [See *Clinical Studies (14.2)* and *Warnings and Precautions (5.7)*.]

2 DOSAGE AND ADMINISTRATION

2.1 Squamous Cell Carcinoma of the Head and Neck

Erbitux in combination with radiation therapy:

- The recommended initial dose is 400 mg/m² administered one week prior to initiation of a course of radiation therapy as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).
- The recommended subsequent weekly dose (all other infusions) is 250 mg/m² infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of radiation therapy (6–7 weeks). Complete Erbitux administration 1 hour prior to radiation therapy.

Erbitux monotherapy:

- The recommended initial dose is 400 mg/m² administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).
- The recommended subsequent weekly dose (all other infusions) is 250 mg/m² infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

2.2 Colorectal Cancer

- The recommended initial dose, either as monotherapy or in combination with irinotecan, is 400 mg/m² administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).
- The recommended subsequent weekly dose, either as monotherapy or in combination with irinotecan, is 250 mg/m² infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

2.3 Recommended Premedication

Premedicate with an H_1 antagonist (eg, 50 mg of diphenhydramine) intravenously 30–60 minutes prior to the first dose; premedication should be administered for subsequent Erbitux doses based upon clinical judgment and presence/severity of prior infusion reactions.

2.4 Dose Modifications

Infusion Reactions

Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC Grades 3–4 infusion reactions.

Immediately and permanently discontinue Erbitux (cetuximab) for serious infusion reactions, requiring medical intervention and/or hospitalization. [See *Warnings and Precautions (5.1)*.]

Dermatologic Toxicity

Recommended dose modifications for severe (NCI CTC Grade 3 or 4) acneform rash are specified in Table 1. [See *Warnings and Precautions (5.4)*.]

Table 1: Erbitux Dose Modification Guidelines for Rash

Severe Acneform Rash	Erbitux	Outcome	Erbitux Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Continue at 250 mg/m² Discontinue Erbitux
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 200 mg/m² Discontinue Erbitux
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 150 mg/m² Discontinue Erbitux
4th occurrence	Discontinue Erbitux		

2.5 Preparation for Administration

Do not administer Erbitux as an intravenous push or bolus.

Administer via infusion pump or syringe pump. Do not exceed an infusion rate of 10 mg/min.

Administer through a low protein binding 0.22-micrometer in-line filter.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, cetuximab particulates. **Do not shake or dilute.**

3 DOSAGE FORMS AND STRENGTHS

100 mg/50 mL, single-use vial

200 mg/100 mL, single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of Erbitux included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in clinical trials, with fatal outcome in 1 patient.

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Monitor patients for 1 hour following Erbitux infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions.

Immediately and permanently discontinue Erbitux in patients with serious infusion reactions. [See *Boxed Warning* and *Dosage and Administration (2.4)*.]

5.2 Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and Erbitux as compared to none of 212 patients treated with radiation therapy alone in a randomized, controlled trial in patients with SCCHN. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of Erbitux. One patient with no prior history of coronary artery disease died one day after the last dose of Erbitux. Carefully consider use of Erbitux in combination with radiation therapy in head and neck cancer patients with a history of coronary artery disease,

congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux (cetuximab). [See *Boxed Warning* and *Warnings and Precautions (5.6)*.]

5.3 Pulmonary Toxicity

Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving Erbitux in clinical trials. Interrupt Erbitux for acute onset or worsening of pulmonary symptoms. Permanently discontinue Erbitux for confirmed ILD.

5.4 Dermatologic Toxicity

Dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, cheilitis), and hypertrichosis occurred in patients receiving Erbitux therapy. Acneform rash occurred in 76–88% of 1373 patients receiving Erbitux in clinical trials. Severe acneform rash occurred in 1–17% of patients.

Acneform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Monitor patients receiving Erbitux for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during Erbitux therapy. [See *Dose Modifications (2.4)*.]

5.5 Use of Erbitux in Combination With Radiation and Cisplatin

The safety of Erbitux in combination with radiation therapy and cisplatin has not been established. Death and serious cardiotoxicity were observed in a single-arm trial with Erbitux, radiation therapy, and cisplatin (100 mg/m^2) in patients with locally advanced SCCHN. Two of 21 patients died, one as a result of pneumonia and one of an unknown cause. Four patients discontinued treatment due to adverse events. Two of these discontinuations were due to cardiac events.

5.6 Hypomagnesemia and Electrolyte Abnormalities

In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients (199/365) receiving Erbitux and was severe (NCI CTC Grades 3 and 4) in 6–17%. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of Erbitux. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of Erbitux. Replete electrolytes as necessary.

5.7 Epidermal Growth Factor Receptor (EGFR) Expression and Response

Because expression of EGFR has been detected in nearly all SCCHN tumor specimens, patients enrolled in the head and neck cancer clinical studies were not required to have immunohistochemical evidence of EGFR tumor expression prior to study entry.

Patients enrolled in the colorectal cancer clinical studies were required to have immunohistochemical evidence of EGFR tumor expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak-to-moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Infusion reactions [See *Boxed Warning* and *Warnings and Precautions (5.1)*.]
- Cardiopulmonary arrest [See *Boxed Warning* and *Warnings and Precautions (5.2)*.]
- Pulmonary toxicity [See *Warnings and Precautions (5.3)*.]
- Dermatologic toxicity [See *Warnings and Precautions (5.4)*.]
- Hypomagnesemia and Electrolyte Abnormalities [See *Warnings and Precautions (5.6)*.]

The most common adverse reactions with Erbitux (incidence ≥25%) are cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

The most serious adverse reactions with Erbitux are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.

Across all studies, Erbitux was discontinued in 3–10% of patients because of adverse reactions.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Erbitux in 1373 patients with colorectal cancer or SCCHN in randomized Phase 3 (Studies 1 and 3) or Phase 2 (Studies 2 and 4) trials treated at the recommended dose and schedule for a median of 7 to 14 weeks. [See *Clinical Studies (14)*.]

Infusion reactions: Infusion reactions, which included pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in 15–21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of patients; infusion reactions were fatal in 1 patient.

Infections: The incidence of infection was variable across studies, ranging from 13–35%. Sepsis occurred in 1–4% of patients.

Renal: Renal failure occurred in 1% of patients with colorectal cancer.

Squamous Cell Carcinoma of the Head and Neck

Table 2 contains selected adverse events in 420 patients receiving radiation therapy either alone or with Erbitux (cetuximab) for locally or regionally advanced SCCHN in Study 1. Erbitux was administered at the recommended dose and schedule (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 8 infusions (range 1–11).

Table 2: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

Body System Preferred Term	Erbitux plus Radiation (n=208) Grades 1–4	 Grades 3 and 4	Radiation Therapy Alone (n=212) Grades 1–4	 Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia	56	4	49	5
Fever[1]	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction[2]	15	3	2	0
Infection	13	1	9	1
Chills[1]	16	0	5	0
Digestive				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Alanine Transaminase, high[3]	43	2	21	1
Aspartate Transaminase, high[3]	38	1	24	1
Alkaline Phosphatase, high[3]	33	<1	24	0
Respiratory				
Pharyngitis	26	3	19	4
Skin/Appendages				
Acneform Rash[4]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

[1] Includes cases also reported as infusion reaction.

[2] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever", or "dyspnea".

[3] Based on laboratory measurements, not on reported adverse events, the number of subjects with tested samples varied from 205–206 for Erbitux plus Radiation arm; 209–210 for Radiation alone.

[4] Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis".

The incidence and severity of mucositis, stomatitis, and xerostomia were similar in both arms of the study.

Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in Erbitux in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%). The incidence of Grade 3 or 4 late radiation toxicities was similar between the radiation therapy alone and the Erbitux plus radiation treatment groups.

Colorectal Cancer

Table 3 contains selected adverse events in 562 patients receiving best supportive care (BSC) alone or with Erbitux (cetuximab) monotherapy for metastatic colorectal cancer in Study 3. Erbitux was administered at the recommended dose and schedule (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly).

Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma[1] Treated with Erbitux Monotherapy

	Erbitux plus BSC (n=288)		BSC alone (n=274)	
Body System Preferred Term	Any Grades[2]	Grades 3 and 4	Any Grades	Grades 3 and 4
	% of Patients			
Dermatology				
Rash/Desquamation	89	12	16	<1
Dry Skin	49	0	11	0
Pruritus	40	2	8	0
Other-Dermatology	27	1	6	1
Nail Changes	21	0	4	0
Body as a Whole				
Fatigue	89	33	76	26
Fever	30	1	18	<1
Infusion Reactions[3]	20	5		
Rigors, Chills	13	<1	4	0
Pain				
Abdominal Pain	59	14	52	16
Pain-Other	51	16	34	7
Headache	33	4	11	0
Bone Pain	15	3	7	2
Pulmonary				
Dyspnea	48	16	43	12
Cough	29	2	19	1
Gastrointestinal				
Constipation	46	4	38	5
Diarrhea	39	2	20	2
Vomiting	37	6	29	6
Stomatitis	25	1	10	<1
Other-Gastrointestinal	23	10	18	8
Mouth Dryness	11	0	4	0
Infection				
Infection without neutropenia	35	13	17	6
Neurology				
Insomnia	30	1	15	1
Confusion	15	6	9	2
Anxiety	14	2	8	1
Depression	13	1	6	<1

[1] Adverse reactions occurring more frequently in Erbitux treated patients compared with controls.

[2] Adverse events were graded using the NCI CTC, V 2.0.

[3] Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, pruritus, sweating, tremors, shaking, cough, visual disturbances, or other) recorded by the investigator as infusion related.

BSC = best supportive care

The most frequently reported adverse events in 354 patients treated with Erbitux plus irinotecan in clinical trials were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common Grades 3–4 adverse events included diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneform rash (14%).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenic responses to cetuximab were assessed using either a double antigen radiometric assay or an ELISA assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving Erbitux (cetuximab) has not been adequately determined. Non-neutralizing anti-cetuximab antibodies were detected in 5% (49 of 1001) of evaluable patients without apparent effect on the safety or antitumor activity of Erbitux.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Erbitux with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

A drug interaction study was performed in which Erbitux was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between Erbitux and irinotecan.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Erbitux in pregnant women. Based on animal models, EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Human IgG is known to cross the placental barrier; therefore, Erbitux may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. Erbitux should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnant cynomolgus monkeys were treated weekly with 0.4 to 4 times the recommended human dose of cetuximab (based on body surface area) during the period of organogenesis (gestation day [GD] 20–48). Cetuximab was detected in the amniotic fluid and in the serum of embryos from treated dams at GD 49. No fetal malformations or other teratogenic effects occurred in offspring. However, significant increases in embryolethality and abortions occurred at doses of approximately 1.6 to 4 times the recommended human dose of cetuximab (based on total body surface area).

8.3 Nursing Mothers

It is not known whether Erbitux is secreted in human milk. IgG antibodies, such as Erbitux, can be excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Erbitux, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If nursing is interrupted, based on the mean half-life of cetuximab [see *Clinical Pharmacology (12.3)*], nursing should not be resumed earlier than 60 days following the last dose of Erbitux.

8.4 Pediatric Use

The safety and effectiveness of Erbitux in pediatric patients have not been established. The pharmacokinetics of cetuximab have not been studied in pediatric populations.

8.5 Geriatric Use

Of the 1062 patients who received Erbitux with irinotecan or Erbitux monotherapy in five studies of advanced colorectal cancer, 363 patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Clinical studies of Erbitux conducted in patients with head and neck cancer did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 208 patients with head and neck cancer who received Erbitux with radiation therapy, 45 patients were 65 years of age or older.

10 OVERDOSAGE

The maximum single dose of Erbitux administered is 1000 mg/m^2 in one patient. No adverse events were reported for this patient.

11 DESCRIPTION

Erbitux is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). Cetuximab is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. Cetuximab is produced in mammalian (murine myeloma) cell culture.

Erbitux is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Erbitux is supplied at a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use vials. Cetuximab is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor–alpha. *In vitro* assays and *in vivo* animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. *In vitro*, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

12.3 Pharmacokinetics

Erbitux (cetuximab) administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m² as the dose increased from 20 to 200 mg/m², and at doses >200 mg/m², it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m².

Following the recommended dose regimen (400 mg/m² initial dose; 250 mg/m² weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were similar in patients with SCCHN and those with colorectal cancer.

Based on a population pharmacokinetic analysis, female patients with colorectal cancer had a 25% lower intrinsic clearance of cetuximab than male patients. Qualitatively similar, but smaller gender differences in cetuximab clearance were observed in patients with SCCHN. The gender differences in clearance do not necessitate any alteration of dosing because of a similar safety profile.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to test cetuximab for carcinogenic potential, and no mutagenic or clastogenic potential of cetuximab was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. Menstrual cyclicity was impaired in female cynomolgus monkeys receiving weekly doses of 0.4 to 4 times the human dose of cetuximab (based on total body surface area). Cetuximab-treated animals exhibited increased incidences of irregular or absent cycles, as compared to control animals. These effects were initially noted beginning week 25 of cetuximab treatment and continued through the 6-week recovery period. In this same study, there were no effects of cetuximab treatment on measured male fertility parameters (ie, serum testosterone levels and analysis of sperm counts, viability, and motility) as compared to control male monkeys. It is not known if cetuximab can impair fertility in humans.

13.2 Animal Pharmacology and/or Toxicology

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

14 CLINICAL STUDIES

14.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Study 1 was a randomized, multicenter, controlled trial of 424 patients with locally or regionally advanced SCCHN. Patients with Stage III/IV SCCHN of the oropharynx, hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive either Erbitux plus radiation therapy or radiation therapy alone. Stratification factors were Karnofsky Performance Status (60–80 versus 90–100), nodal stage (N0 versus N+), tumor stage (T1–3 versus T4 using American Joint Committee on Cancer 1998 staging criteria), and radiation therapy fractionation (concomitant boost versus once-daily versus twice-daily). Radiation therapy was administered for 6–7 weeks as once daily, twice daily, or concomitant boost. Erbitux was administered as a 400 mg/m² initial dose beginning one week prior to initiation of radiation therapy, followed by 250 mg/m² weekly administered 1 hour prior to radiation therapy for the duration of radiation therapy (6–7 weeks).

Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were Caucasian, and 90% had baseline Karnofsky Performance Status ≥80. There were 258 patients enrolled in US sites (61%). Sixty percent of patients had oropharyngeal, 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen.

The main outcome measure of this trial was duration of locoregional control. Overall survival was also assessed. Results are presented in Table 4.

Table 4: Study 1: Clinical Efficacy in Locoregionally Advanced SCCHN

	Erbitux + Radiation (n=211)	Radiation Alone (n=213)	Hazard Ratio (95% CI[a])	Stratified Log-rank p-value
Locoregional control				
Median duration (months)	24.4	14.9	0.68 (0.52–0.89)	0.005
Overall survival				
Median duration (months)	49.0	29.3	0.74 (0.57–0.97)	0.03

[a] CI = confidence interval

Study 2 was a single-arm, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN. All patients had documented disease progression within 30 days of a platinum-based chemotherapy regimen. Patients received a 20-mg test dose of Erbitux (cetuximab) on Oay 1, followed by a 400-mg/m² initial dose, and 250 mg/m² weekly until disease progression or unacceptable toxicity.

The median age was 57 years, 82% were male, 100% Caucasian, and 62% had a Karnofsky Performance Status of ≥80.

The objective response rate was 13% (95% confidence interval 7%–21%). Median duration of response was 5.8 months (range 1.2–5.8 months).

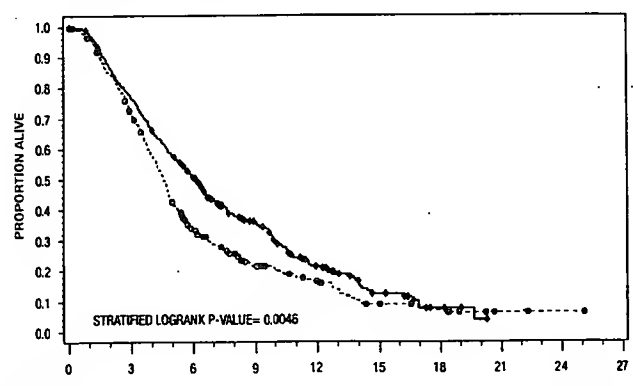
14.2 Colorectal Cancer

Study 3 was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent, metastatic colorectal cancer. Patients were randomized (1:1) to receive either Erbitux plus best supportive care (BSC) or BSC alone. Erbitux was administered as a 400-mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity.

Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were Caucasian, and 77% had baseline ECOG Performance Status of 0–1. All patients were to have received and progressed on prior therapy including an irinotecan-containing regimen and an oxaliplatin-containing regimen.

The main outcome measure of the study was overall survival. The results are presented in Figure 1.

Figure 1: Kaplan Meier Curve for Overall Survival in Patients with Metastatic Colorectal Cancer



SUBJECTS AT RISK										
CET+BSC	287	217	136	78	37	14	4	0	0	0
BSC	285	197	85	44	26	12	8	2	1	0

——— CETUXIMAB + BSC   ◦◦◦ CENSORED   - - - - BSC   ••• CENSORED

GROUP	# DEAD / # RANDOMIZED	MEDIAN (95% CI)	HAZARD RATIO (95.00% CI)
CETUXIMAB + BSC	222/287	6.14 (5.36 - 6.70)	
BSC	234/285	4.57 (4.21 - 4.86)	
CETUXIMAB + BSC OVER BSC			0.77 (0.64 - 0.92)

Study 4 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent metastatic colorectal cancer. Patients were randomized (2:1) to receive either Erbitux plus irinotecan (218 patients) or Erbitux monotherapy (111 patients). Erbitux was administered as a 400-mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity. In the Erbitux plus irinotecan arm, irinotecan was added to Erbitux using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m² weekly times four doses every 6 weeks. Of the 329 patients, the median age was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline Karnofsky Performance Status ≥80. Approximately two-thirds had previously failed oxaliplatin treatment.

The efficacy of Erbitux plus irinotecan or Erbitux monotherapy, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In patients receiving Erbitux plus irinotecan, the objective response rate was 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months, and median time to progression was 4.1 months. In patients receiving Erbitux monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%), median duration of response was 4.2 months, and median time to progression was 1.5 months. Similar response rates were observed in the pre-defined subsets in both the combination arm and monotherapy arm of the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

Erbitux® (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, preservative-free, injectable liquid.

NDC 66733-948-23 100 mg/50 mL, single-use vial, individually packaged in a carton

NDC 66733-958-23 200 mg/100 mL, single-use vial, individually packaged in a carton

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **Do not freeze.** Increased particulate formation may occur at temperatures at or below 0° C. This product contains no preservatives. Preparations of Erbitux in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To report signs and symptoms of infusion reactions such as fever, chills, or breathing problems.
- Of the potential risks of using Erbitux during pregnancy or nursing and of the need to use adequate contraception in both males and females during and for 6 months following the last dose of Erbitux therapy.
- That nursing is not recommended during, and for 2 months following the last dose of Erbitux therapy.
- To limit sun exposure (use sunscreen, wear hals) while receiving and for 2 months following the last dose of Erbitux.

Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876
Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543

ImClone Systems Incorporated   Bristol-Myers Squibb

1236886A4
ER-80001-11-08   Rev November 2008